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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/692,439	10/22/2003	David J. Pinsky	51917-CB-PCT-US/JPW/AJM/A	8415

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EXAMINER	
SZPERKA, MICHAEL EDWARD	
ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
12/03/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	Application No. 10/692,439	Applicant(s) PINSKY ET AL.	
	Examiner Michael Szperka	Art Unit 1644	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 09 November 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: 25.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:
    See attached .
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

Michael Szperka, Ph.D.
Patent Examiner
Art Unit: 1644
11/29/07

DETAILED ACTION

1. Applicant's arguments received November 9, 2007 are acknowledged.

Claims 1-24 and 26-35 have been canceled.

Claim 25 is pending in the instant application.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claim 25 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Toledo-Pereyra (Klin Wochenschr, 1991, 69:1099-1104) in view of Benedict et al. (of record on the 9/20/04 IDS) and in view of the product use sheet from 1,5-dansyl-Glu-Gly-Arg chloromethyl ketone from Calbiochem (revision 27 May 1997) for the reasons of record.

The office action mailed August 7, 2007 states:

> Toledo-Pereyra discloses that at the time the instant invention was made, a skilled artisan knew that "reperfusion injury" was often referred to by the descriptive physiological pathological process of thrombosis (see entire document, particularly the right column of page 1099). Toledo-Pereyra further discloses that fibrinogen activation and clotting (i.e. thrombosis) is a pathophysiological event in reperfusion injury that needs to be treated with pharmacological agents such as heparin to inhibit coagulation (see particularly the right column of page 1099, Table 7, and the right column of page 1103). These teachings differ from the instant claimed invention in that Toledo-Pereyra does not disclose the administration of "Factor IXa compounds" to treat thrombosis in reperfusion injury.

Benedict et al. disclose that inactivated Factor IXa was successfully used to inhibit thrombus formation in vivo (see entire document, particularly the abstract). They further disclose that administration of inactivated factor IXa offers an advantage over the administration of heparin for inhibiting coagulation in that animals treated with heparin suffered from excessive bleeding while animals given inactivated Factor IXa did not manifest excessive bleeding (see particularly figure 4). Benedict et al. disclose making inhibited factor IXa by incubating factor IXa with glu-gly-arg-chloromethyl ketone (see particularly the right column of page 1760).

The product use sheet from 1,5-dansyl-Glu-Gly-Arg chloromethyl ketone from Calbiochem teaches that the use of a fluorophore (i.e. dansyl) on the enzyme inhibitor allows for direct monitoring of interactions of the labeled enzyme/inhibitor complex.

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to administer inactivated Factor IXa to patients to treat reperfusion injury. Motivation to do so at the time the invention was made comes from the teachings of Toledo-Pereyra that thrombus formation in reperfusion injury is to be treated with heparin and the teachings of Benedict et al. that inactivated Factor IXa is better than heparin at inhibiting thrombus formation in vivo because unlike heparin, inactivated factor IXa administration does not lead to excessive bleeding. A skilled artisan would be further motivated to substitute dansyl-Glu-Gly-Arg chloromethyl ketone for the Glu-Gly-Arg chloromethyl ketone used by Benedict et al. to inhibit factor IXa because the use of a fluorescently labeled inhibitor allows for the monitoring of the interactions that take place with the inhibited enzyme as taught by the Calbiochem product use sheet.

Applicant's arguments filed November 9, 2007 have been fully considered but they are not persuasive. Applicant argues that while the cited prior art teaches that 1,5-dansyl-Glu-Gly-Arg chloromethyl ketone inhibits factor Xa and that Glu-Gly-Arg chloromethyl ketone inhibits factor IXa, the prior art does not teach or suggest that 1,5-dansyl-Glu-Gly-Arg chloromethyl ketone inhibits factor IXa.

This argument is not persuasive because 1,5-dansyl-Glu-Gly-Arg chloromethyl ketone and Glu-Gly-Arg chloromethyl ketone are functional equivalents, differing only in the presence of a fluorescence group (i.e. dansyl). Note that the enzyme inhibiting activity is found in the Glu-Gly-Arg chloromethyl ketone moiety and is not present in dansyl. As such, it would have been obvious to a person of ordinary skill in the art to substitute known equivalents, and such a person would have had additional motivation to do so since use of a fluorescently labeled peptide inhibitor allows for detection of the enzyme/inhibitor complex as disclosed in the product use sheet for 1,5-dansyl-Glu-Gly-Arg chloromethyl ketone. The rejection is maintained.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory

obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claim 25 stands rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-19 of U.S. Patent No. 6,316,403 in view of Toledo-Pereyra (of record) in view of Benedict et al. (of record) and in view of the product use sheet from 1,5-dansyl-Glu-Gly-Arg chloromethyl ketone from Calbiochem (revision 27 May 1997) for the reasons of record.

The office action mailed August 7, 2007 states:

> The claims of the '403 patent recite methods of treating ischemic disorders by administering inactivated factor IX to a patient to inhibit coagulation so as to treat the ischemic disorder in the patient. Dependent claims in the '403 patent recite that factor IX is inactivated at it active site, via chemical inactivation and dansylation (see particularly patented claims 17-19). The claims of the '403 patent differ from the instant claimed invention in that the claims of the '403 patent do not specifically recite reperfusion injury and do not recite that the species of inactivated Factor IX recited in the instant claim.
>
> Toledo-Pereyra discloses that at the time of the instant invention, a skilled artisan would know that "reperfusion injury" is often referred to by the descriptive physiological pathological process of thrombosis (see entire document, particularly the right column of page 1099). Toledo-Pereyra further discloses that fibrinogen activation and clotting (i.e. thrombosis) is a pathophysiological event in reperfusion (see particularly the right column of page 1099 and Table 7 on page 1103).
>
> Benedict et al. disclose that factor IXa inactivated with glu-gly-arg-chloromethyl ketone successfully inhibits thrombus formation in vivo (see entire document, particularly the abstract).
>
> The product use sheet from 1,5-dansyl-Glu-Gly-Arg chloromethyl ketone from Calbiochem teaches that the use of a fluorophore (i.e. dansyl) on the enzyme inhibitor allows for direct monitoring of interactions of the labeled enzyme/inhibitor complex.
>
> Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to administer factor IXa compounds, such as inactivated factor IX and IXa to treat reperfusion injuries. Motivation to do so comes from the teachings of the '403 patent which teaches that "Factor IXa" compounds are to be administered to inhibit thrombosis in a patient, and the teachings of Toledo-Pereyra that thrombosis is an important pathophysiological even that occurs in reperfusion injury. A person of skill in the art would be motivated to use a factor IXa that has been inhibited with dansyl-Glu-Gly-

Arg chloromethyl ketone because Benedict et al. successfully inhibited thrombus formation in vivo using factor IXa inactivated with Glu-Gly-Arg chloromethyl ketone and the Calbiochem product use sheet teaches that use of a labeled inhibitors offers the advantage of being able to detect labeled enzyme/inhibitor complexes.

Applicant's arguments filed November 9, 2007 have been fully considered but they are not persuasive. Specifically, the response received November 9, 2007 does not appear to contain any argument directed to this rejection.

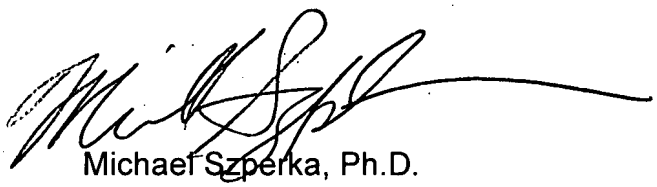
Therefore, applicant's silence concerning this rejection appears to indicate that applicant agrees that the rejection of record is proper. The rejection is maintained.

6. No claim is allowable.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Michael Szperka, Ph.D.
Patent Examiner
Art Unit 1644
November 29, 2007